J. Cosmet. Sci., 54, 537–550 (November/December 2003)

Improving the aqueous solubility of triclosan by solubilization, complexation, and *in situ* salt formation

CHRISTINE GROVE, WILNA LIEBENBERG, JAN L. DU PREEZ, WENZHAN YANG, and MELGARDT M. DE VILLIERS, *School of Pharmacy, Potchefstroom University for Christian Higher Education, Potchefstroom 2520, South Africa (C.G., W.L., J.L.d.P.), and Department of Basic Pharmaceutical Sciences, School of Pharmacy, University of Louisiana at Monroe, Monroe, LA 71209 (W.Y., M.M.d.V.).*

Accepted for publication July 29, 2003.

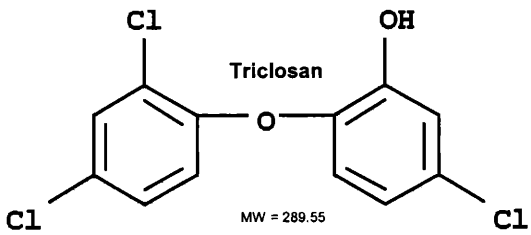
Synopsis

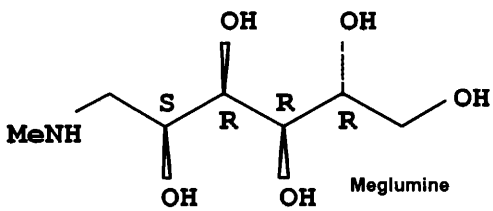
Triclosan, an antimicrobial, although widely incorporated into many skin care products, toothpastes, and liquid soaps, presents formulation difficulties because it is practically insoluble in water. The objective of this study was to improve the aqueous solubility of triclosan through solubilization, complexation, and salt formation. The solubility of triclosan in distilled water and in phosphate buffers (pH 7.4) was determined at 30°C. The order of solubilizing performance of the solubilizers was: N-methylglucamine ≥ L-arginine > sodium lauryl sulfate > β-cyclodextrin ≥ hydroxypropyl-β-cyclodextrin > ethanolamine > sodium benzoate > sodium methyl 4-hydroxybenzoate > triethanolamine ≥ diethanolamine. These solubilizers increased the solubility of triclosan from 80- to 6000-fold. Micellar solubilization and the formation of either salts or complexes are postulated as possible mechanisms for the increase in the solubility of triclosan by the surfactant sodium lauryl sulphate, the cyclic sugar derivatives β-cyclodextrin and 2-hydropropyl-β-cyclodextrin, the amino acid L-arginine, and the amino sugar alcohol N-methylglucamine. Furthermore, although the bacteriostatic efficacy of triclosan was significantly increased when solubilized with N-methylglucamine, L-arginine, and ethanolamine, increased solubilization did not increase the effectiveness of triclosan for all solubilizers tested.

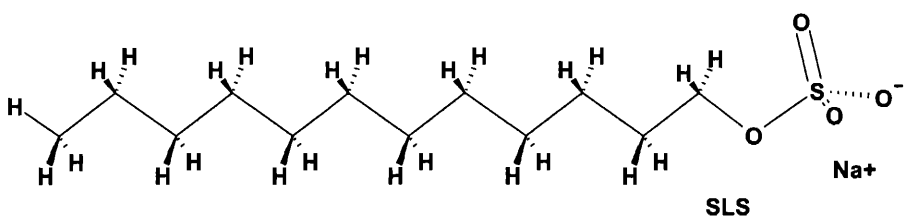
INTRODUCTION

Triclosan, also known as 5-chloro-2-(2,4-dichlorophenoxy) phenol, 2,4,4′-trichloro-2′-hydroxydiphenylether (Figure 1), is an antimicrobial that is incorporated into many skin care products, toothpastes, liquid soaps, carpets, children's toys and plastic kitchenware (1,2). It has antimicrobial activity against gram-negative as well as gram-positive bacteria, under both *in vitro* and *in vivo* conditions (1). It is a white to off-white crystalline powder with a faint aromatic smell, a melting point of 55°–57°C, a pKa of 7.9, and

Address all correspondence to Melgardt M. de Villiers.







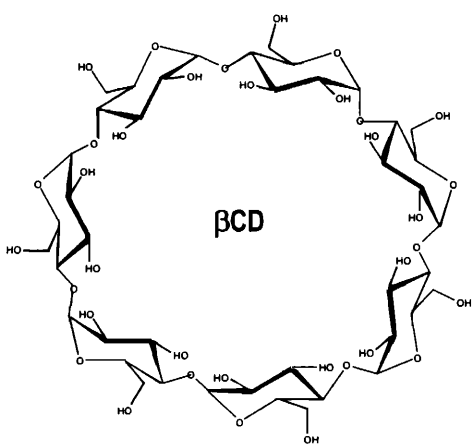


Figure 1. Molecular structures of triclosan, N-methylglucamine, SLS, and βCD.

water solubility $<10^{-6}$ g/ml^{-1}. This lipophilic, anionic compound is compatible with many raw materials and has several dermatological uses (2). Among others, it has beneficial effects on atopic dermatitis (3,4), it reduces eczema (2) and plaque (5,6), and it can eliminate the irritant effects of sodium lauryl sulfate on the skin or buccal/lingual surfaces (6). All these applications make this antibacterial agent very useful for skin care formulations, particularly for surfactant-based hand soaps, hand disinfectants, mouth rinses, and surface cleaners (2). In two reports published in *Nature,* researchers showed that triclosan, far from being a generalized antimicrobial, works more like an antibiotic (7,8). Recently it was also demonstrated that triclosan kills the parasites responsible for malaria and toxoplasmosis, even at very low concentrations (9,10).

Although triclosan is extensively used in cosmetic products and household chemicals, poor aqueous solubility does limit its wider application (11). Usually the poor solubility of lipophilic compounds is increased by solubilization, complexation, or salt formation (12). Savage (1) published a table listing the solubility of triclosan in commonly used solvents. To increase the solubility of triclosan, the compound has also been processed and complexed with various cyclodextrins including β-cyclodextrin (βCD) (11,13), γ-cyclodextrin (γCD) (14), 2-hydropropyl-β-cyclodextrin (HPβCD) (15), and sulfobutyl ether β-cyclodextrin (SBβCD) (13).

In all these studies the anionic triclosan/cationic SBβCD complex increased the solubility of triclosan the most. Triclosan has also been converted to salts such as triclosan monophosphate to increase its solubility (16). In addition to these reports, no other detailed studies describing the enhancement of the aqueous solubility of triclosan have been found in the literature.

In this study we report the effect of various additives on the solubility of triclosan in water. These solubilizing agents included ethanolamine, diethanolamine, triethanolamine, glycine, L-arginine, N-methylglucamine (meglumine), βCD, γCD, HPβCD, sodium benzoate, sodium methyl 4-hydroxybenzoate, and sodium lauryl sulfate (SLS). In addition, the antimicrobial activity of combinations of triclosan and those solubilizers that increased its solubility was compared to the antimicrobial activity of triclosan and the solubilizing agent alone.

MATERIALS AND METHODS

MATERIALS

Triclosan (Irgasan DP 300, Ciba Specialty Chemicals, Basel, Switzerland) was obtained from Adcock Ingram, Ltd. (Krugersdorp, South Africa). Ethanolamine, diethanolamine, triethanolamine, glycine, L-arginine, N-methylglucamine, βCD, γCD, sodium benzoate, sodium methyl 4-hydroxybenzoate, and SLS were obtained from Sigma Chemical Company (St. Louis, MO). HPβCD was obtained from Janssen Biotech (Brussels, Belgium). All other solvents and chemicals were analytical grade and were used as received.

SOLUBILITY MEASUREMENTS

The solubility of triclosan was determined in distilled deionized water and in a 0.1 M phosphate buffer, pH 7.4 (8.62 grams of sodium phosphate dibasic and 5.42 grams of sodium phosphate monobasic in one liter of Milli-Q grade water) containing increasing concentrations ranging from 0–0.2 M of βCD, γCD, HPβCD, and sodium lauryl sulfate, and 0–1.0 M of sodium benzoate, ethanolamine, N-methylglucamine, D-(+)-

glucosamine, diethanolamine, triethanolamine, glycine, L-arginine, and methyl 4-hydroxybenzoate sodium. Triclosan sufficient to ensure saturation was suspended in 10 ml of water or buffer containing increasing amounts of the solubilizers. Duplicate samples were rotated end to end in test tubes with screw caps at 30°C for 48 hours to reach equilibrium. The solubility was measured at 30°C because at this temperature it was easier to control temperature fluctuations during testing and sampling. Suspensions were passed through a 0.45-μm filter (Osmonics, Minnetonka, MN), and the amount of triclosan dissolved in the filtered solutions was determined by HPLC.

HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC)

The HPLC method used in this study complied with specifications for precision, accuracy, selectivity, linearity, and ruggedness as required by the USP XXIV (16). The following reagents and equipment were used: a Hewlett Packard 1050 high-performance liquid chromotographer (Agilent Technologies, Palo Alto, CA), equipped with a variable wavelength UV detector, pump, injection device, and computerized data analysis system, and a Luna C_{18} column (2 μm, 150 × 4.6 mm; Phenomenex, Torrance, CA), controlled at ±20°C. The mobile phase was a mixture of methanol:water (85:15) containing 0.1% H_3PO_4. The flow rate was 1.0 ml/min^{-1}, the injection volume was 10 μl, and the UV detection was at 210 nm.

A triclosan calibration curve was prepared from a series of diluted triclosan solutions that were prepared by dissolving 10 mg of triclosan, accurately weighed, in 100 ml of methanol with the aid of an ultrasonic bath. From this solution, several dilutions ranging from 10 μg/ml^{-1} to 250 μg/ml^{-1} were prepared. A calibration curve of the area under the curve (AUC) *versus* concentration was linear [$y = 70875x + 94.649$ ($R^2 = 0.9998$)] and was used to determine the concentration of triclosan in unknown solutions. Examples of chromatograms are shown in Figure 2.

ANTIMICROBIOLOGICAL ACTIVITY

Samples were sent to the SABS (South African Bureau of Standards, Pretoria, South Africa) where zone inhibition tests were performed on the samples (SABS method 730: Antibacterial Efficacy of Solid and Semi-Solid Antiseptics). Organisms tested against were *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aereus, Aspergillus niger,* and *Candida albicans.* The following method was used: First, the triclosan powder was tested. Then the solubilizers in water and in buffer without triclosan were tested to determine the antimicrobial activity of each of the solubilizers alone. Afterwards, solutions containing the highest possible common concentration of triclosan that could be dissolved in all the solubilizer solutions were tested for antimicrobial activity. For example: A saturated solution of triclosan in an aqueous 1.0 M N-methylglucamine solution was prepared and the concentration of triclosan determined by HPLC. This was repeated for all the solubilizers at various concentrations. Based on these results, the highest common concentration that could be dissolved in each of the solubilizer solutions was determined. Solutions containing this concentration of triclosan, the equivalent amounts of the solubilizer in water, and the buffer at pH 7.4 were prepared and tested for antimicrobial activity. The antimicrobial activity of solutions containing only the solubilizers at the

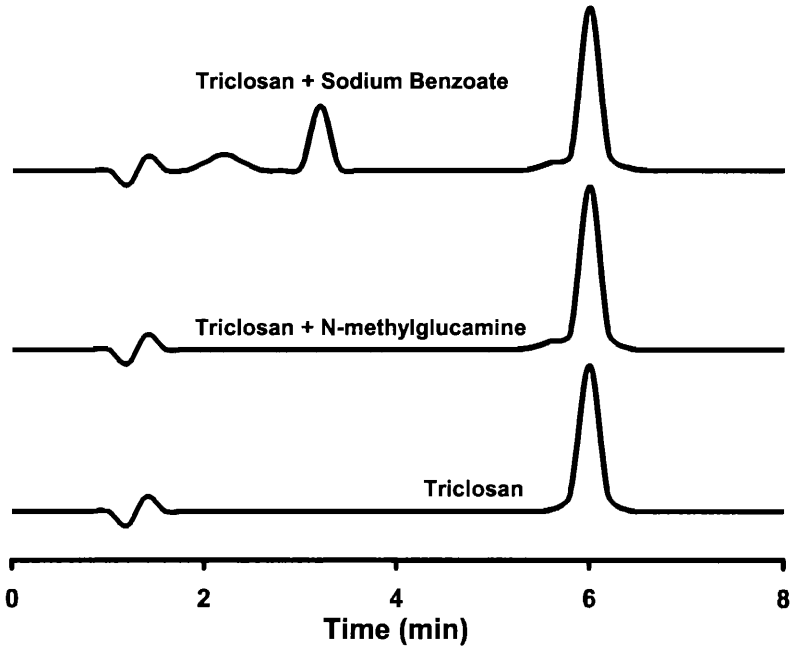


Figure 2. HPLC chromatograms of triclosan and triclosan solubilizer mixtures.

desired concentrations was also tested. The aim of these tests was to determine if the antimicrobial activity of triclosan was influenced by the solubilizers.

ZONE INHIBITION TEST (SABS SM 730:1975): ANTIBACTERIAL EFFICACY OF SOLID AND SEMISOLID ANTISEPTICS

This test determined the ability of the triclosan solutions to inhibit the growth of *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aereus, Aspergillus niger,* and *Candida albicans.* Sterile molten TS agar was prepared and allowed to cool to 45°C. While the agar was left to cool, 0.1 ml of solutions containing the respective microorganisms were pipetted into sterile petri dishes. The agar was poured into the petri dishes and swirled to mix the agar and the microorganisms. The plates were left to cool and set, and then the agar was incubated for two hours at 37°C. A cork bore was used to make holes in the agar in the middle of each petri dish. The bottom of the holes was sealed with molten agar to stop diffusion of the liquid test products underneath the agar. Approximately 0.1 ml of the test solution prepared as described in the previous paragraph was poured into the holes, and then the plates were incubated for 48 hours at 37°C. This test measures the ability of triclosan solutions to diffuse into the agar and kill the microorganisms. After incubation, Vernier caliper was used to measure the angular radius of the zone that formed around the hole.

STATISTICAL ANALYSIS

All calculations were performed in Microsoft Excel (Microsoft, Seattle, WA). Multivariate analysis of variance (MANOVA), including a *post hoc* comparison using the Newman-

Keuls test, was performed on the mean inhibition zones and mean solubility values to identify significant differences in solubility and antibacterial activity (Statitica 5.1, Statsoft Inc., Tulsa, OK). *P*-values of less than 0.05 indicated significant differences in solubility.

RESULTS AND DISCUSSION

Triclosan (Figure 1) belongs to a class of compounds known as hydroxydiphenyl ethers. It is an anionic, lipophilic compound that is very poorly soluble in water. In this study, the solubility in water and pH 7.4 phosphate buffer was determined to be 0.002 mg/ml^{-1} and 0.004 mg/ml^{-1} at 30°C. In Figures 3 and 4 solubility profiles of triclosan in combination with increasing concentrations of three cyclodextrins and SLS are given. Previous researchers have reported the effect of cyclodextrins on the solubility of triclosan (11,13–15). The results are given here as a basis for comparison, to evaluate the effect of other solubilizing agents on the solubility of triclosan.

COMPLEXATION WITH CYCLODEXTRINS

βCD and HPβCD both significantly increased the solubility of triclosan in water and the phosphate buffer (2000- to 4000-fold, Table I). Both cyclodextrins are soluble in water, but HPβCD is more soluble because substitution of the hydroxyl groups of the βCD disrupts the network of hydrogen bonding around the rim of the βCD. As a result of disruption of the hydrogen-bonding network, the hydroxyl groups interact much more strongly with water, resulting in increased solubility compared to βCD. Each

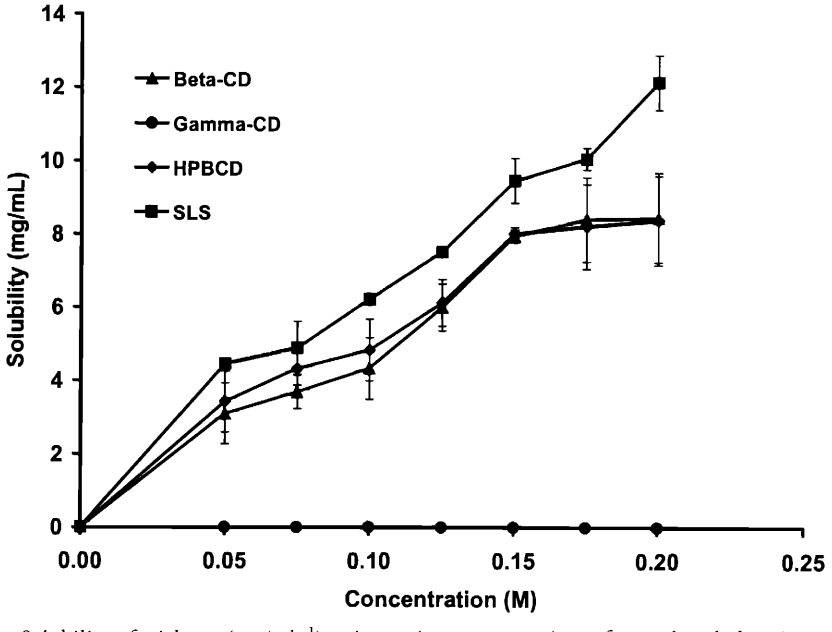


Figure 3. Solubility of triclosan (mg/ml^{-1}) at increasing concentrations of several cyclodextrins and SLS in water. The data points and error bars represent the mean and standard deviations of two replicates.

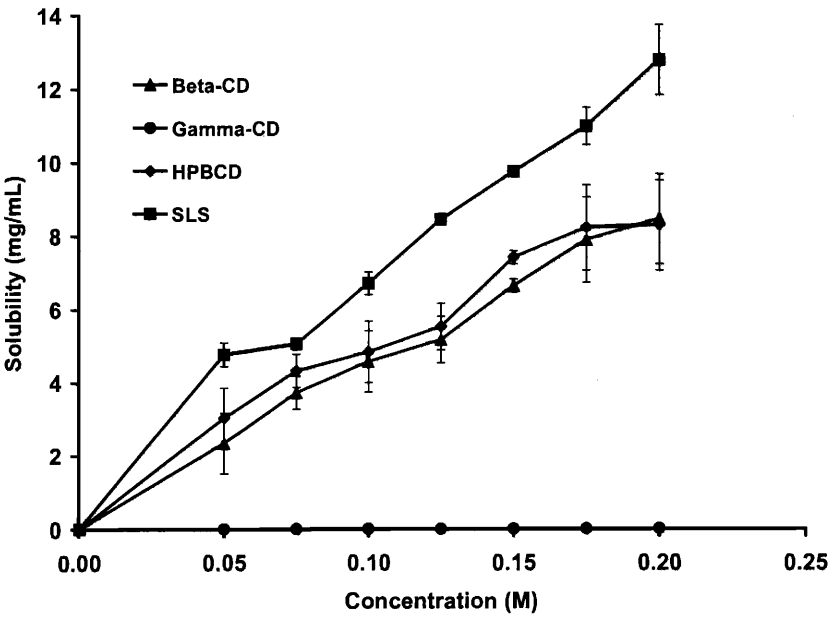


Figure 4. Solubility of triclosan (mg/ml^{-1}) at increasing concentrations of several cyclodextrins and SLS in pH 7.4 phosphate buffer. The data points and error bars represent the mean and standard deviations of two replicates.

Table I
Maximum Solubility of Triclosan in Aqueous and Buffered Solubilizer Solutions With Corresponding Solubilizer Concentrations

	Water		Phosphate buffer (pH 7.4)	
Solubilizer	Solubilizer (M)	Triclosan* (mg/ml^{-1})	Solubilizer (M)	Triclosan (mg/ml^{-1})
N-methylglucamine	1.00**	12.43 ± 1.21	1.00**	18.34 ± 0.62
L-arginine	1.00**	12.81 ± 1.09	0.70	18.35 ± 1.13
SLS	1.00**	12.15 ± 0.75	1.00**	12.77 ± 0.95
βCB	0.15**	8.11 ± 0.79	0.18**	7.89 ± 0.81
HPβCD	0.15	8.20 ± 0.81	0.18	8.21 ± 1.16
Ethanolamine	0.80	5.84 ± 0.37	0.80	6.00 ± 0.27
Sodium benzoate	0.80	5.95 ± 0.40	0.80	2.20 ± 0.16
Na-methylparaben	0.80	3.61 ± 0.34	0.80	3.42 ± 0.43
Triethanolamine	0.80	1.92 ± 0.07	0.80	1.23 ± 0.08
Diethanolamine	0.80	1.43 ± 0.09	0.80	0.98 ± 0.13
Glycine	0.80	0.22 ± 0.01	0.80	0.32 ± 0.01
γCD	0.15	1.10 ± 0.08	0.15	0.13 ± 0.06

* Solubility of triclosan at 30°C was 0.002 mg/ml^{-1} in water and 0.004 mg/ml^{-1} in pH 7.4 buffer.
** Maximum solubility not reached.

cyclodextrin molecule is composed of a ring of glucose molecules (Figure 1), which can accept a lipophilic guest such as triclosan within the ring. A variety of noncovalent forces, such as van der Waal forces, hydrophobic interaction, and dipole moment are responsible for formation of a stable complex. For triclosan, most probably the hydrophobic portion of the guest interacts with the hydrophobic cavity of the cyclodextrin.

For the triclosan cyclodextrin complex, water should be the preferred solvent for complexation because the triclosan molecule that complexes with the cavity of the cyclodextrin is nonpolar and prefers the nonpolar environment of the cavity rather than the polar aqueous environment. As a result, water provides a driving force for complexation in addition to dissolving or dispersing the cyclodextrin and guest. Because of the high solubility of βCD and HPβCD, the complexes are also very soluble. In Table I the maximum solubilities obtained by cyclodextrin complexation with triclosan are listed. There is not a significant difference between the solubility obtained with βCD and HPβCD in both water and pH 7.4 buffer. Contrary to earlier reports in this study, the less soluble γCD was not an effective solubilizer of triclosan (14).

SOLUBILIZATION WITH SLS

As shown in Figures 3 and 4, SLS was an even more effective solubilizing agent than βCD and HPβCD for triclosan. Solubilization of triclosan by this anionic surfactant (Figure 1) occurs through the formation of micelles because when present in a sufficient concentration (above the critical micelle concentration), SLS forms micellar aggregates with hydrophobic, organic tails in the center and anionic polar groups on the outside. These micelles trap in or between their hydrophobic cores the lipophilic triclosan molecules that enhance the solubility of triclosan by several orders of magnitude (3000- to 6000-fold, Table I). Within the experimental parameters used in this study, the increase in the solubility of triclosan achieved with SLS did not reach a plateau (Figures 3 and 4). This suggests that a further increase in the concentration of SLS could increase the solubility of triclosan even more. However, because of excessive foaming, it was difficult to analyze highly concentrated SLS solutions.

SOLUBILIZATION BY AMINO ALCOHOLS AND AMINO ACIDS

Based on previous reports on the solubilization of drug molecules with amino alcohols (17,18), in this study the effect of ethanolamine, diethanolamine, triethanolamine, D(+)glucosamine, and N-methylglucamine on the solubility of triclosan was investigated. Figures 5 and 6 are solubility profiles for triclosan when combined with these amino alcohols. D(+)glucosamine was discarded early during preliminary tests because of its poor solubilizing performance. The order in which these compounds increased the solubility of triclosan (Table I) was N-methylglucamine > ethanolamine > triethanolamine ≥ diethanolamine, both in water and solutions buffered at pH 7.4. In both these media, the solubilization power of N-methylglucamine significantly surpassed that of the other amines, βCD and HPβCD, and SLS.

N-methylglucamine is a derivative of sorbitol in which the hydroxyl group in position 1 is replaced by a methylamino group (Figure 1). This compound is most often used in conjunction with iodinated organic compounds as a contrast medium. The increased solubility of triclosan achieved by the amino alcohols may be attributed to the *in situ* formation of either a salt or a complex (17,18). It is assumed that the formation of these association compounds occurs between the electronegative nitrogen of the amines and the enolic hydrogen of triclosan. This complex is similar to other complexes formed between the electron-donating oxygen of polyethylene glycols and the acidic hydrogen

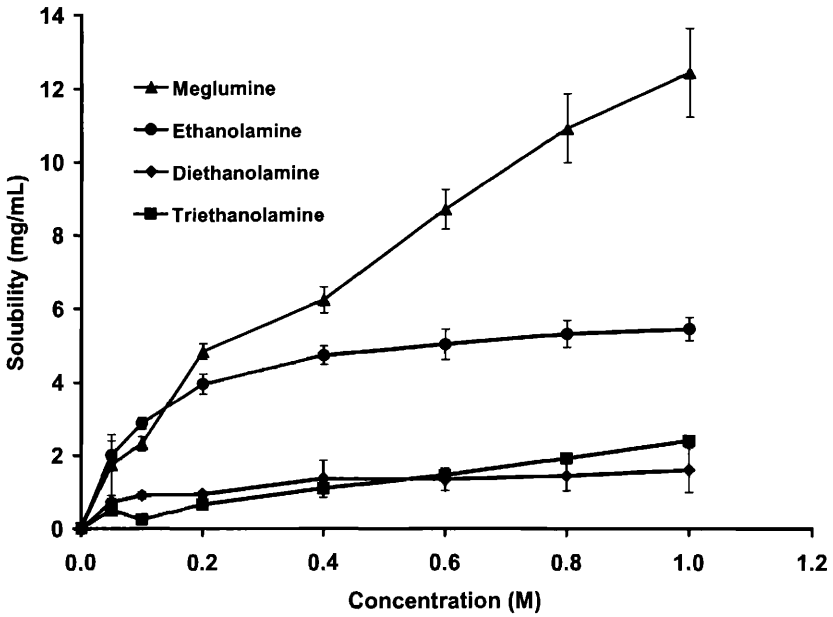


Figure 5. Solubility of triclosan (mg/ml^{-1}) at increasing concentrations of several amino alcohols in water. The data points and error bars represent the mean and standard deviations of two replicates.

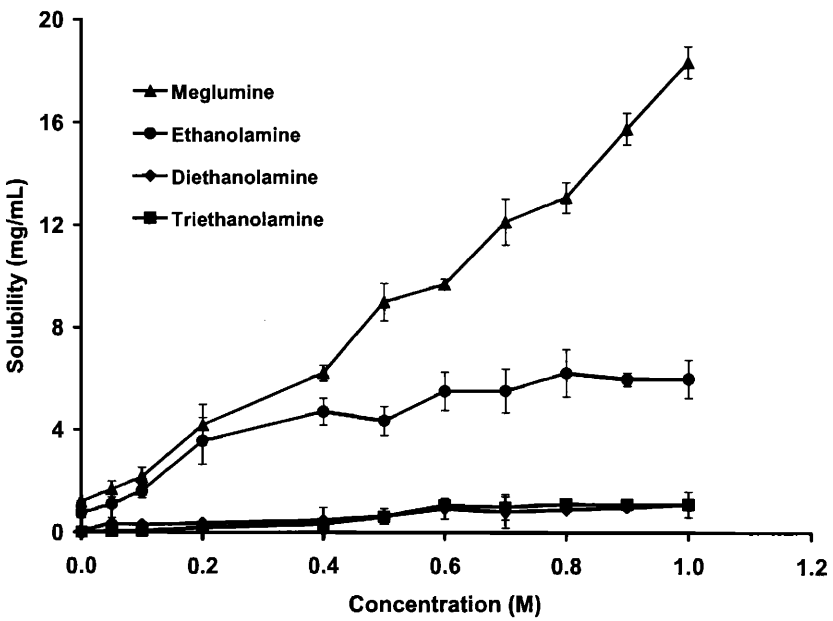


Figure 6. Solubility of triclosan (mg/ml^{-1}) at increasing concentrations of several amino alcohols in pH 7.4 phosphate buffer. The data points and error bars represent the mean and standard deviations of two replicates.

of drugs such as phenobarbital (17). Such a triclosan/amino alcohol complex will form hydrogen bonds with water molecules through the hydrophilic hydroxyl groups of the alcohol moiety to increase the water solubility. In this study, it was not possible to

isolate these association complexes from solution. This provides some indication of the instability of these complexes.

Although slight increases in the pH of the media resulted from an increase in amino alcohol concentration, solubilization of triclosan by this increase in pH was not significant because even higher concentrations of triclosan were achieved in solutions buffered at pH 7.4 (Table I). At a concentration of 1.0 M N-methylglucamine (Table I), the solubility of triclosan in the phosphate-buffered solution was ≈50% higher than in water. This phenomenon could be attributed to an increase in the solvent activity caused by the buffer salts in combination with N-methylglucamine (salting-in), leading to an increase in the solubility of the complexes (19). The same media-dependent increase in solubility was not observed with the other amino alcohols but was observed for L-arginine.

Figures 7 and 8 represent solubility profiles of triclosan in combination with two highly water-soluble amino acids and two water-soluble preservatives. The two preservatives, sodium benzoate and sodium methyl 4-hydroxybenzoate, increased the solubility of triclosan, but this increase was not as significant as that obtained with N-methylglucamine, βCD, HPβCD, and SLS. However, the combination of these preservatives with triclosan could prove useful for the formulation of products where preservative combinations might reduce the chance of bacterial resistance. The acidic amino acid glycine (Figure 7) did not increase the solubility of triclosan, but the strongly alkaline L-arginine did increase the solubility of triclosan in aqueous solutions. The mechanism whereby it increases the solubility of triclosan is probably similar to that of N-methylglucamine because of structural similarities, especially the amine groups (10).

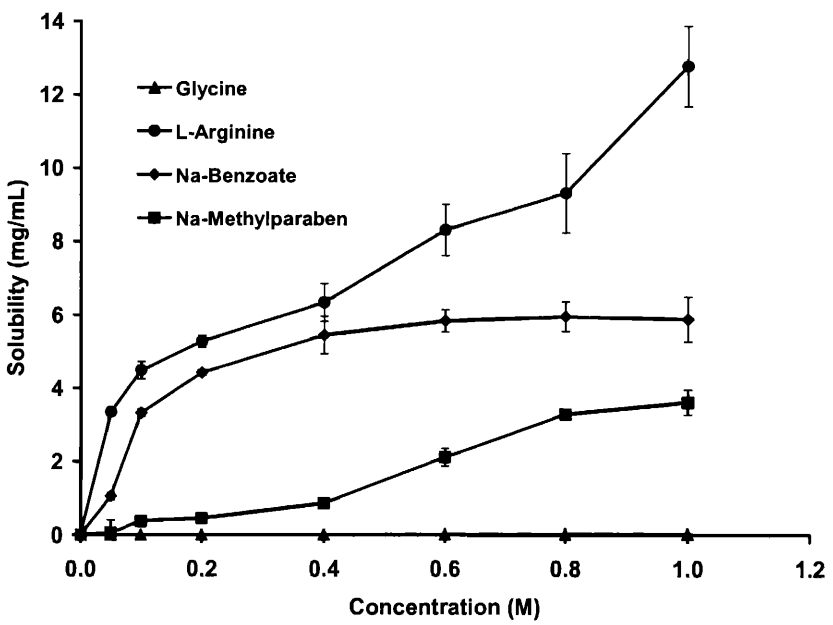


Figure 7. Solubility of triclosan (mg/ml^{-1}) at increasing concentrations of two amino acids and other preservatives in water. The data points and error bars represent the mean and standard deviations of two replicates.

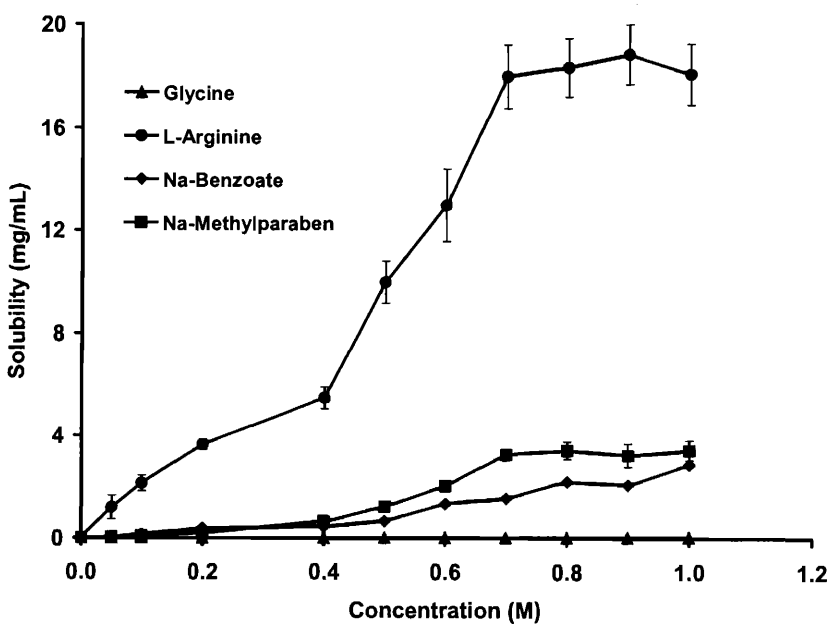


Figure 8. Solubility of triclosan (mg/ml^{-1}) at increasing concentrations of two amino acids and other preservatives in pH 7.4 phosphate buffer. The data points and error bars represent the mean and standard deviations of two replicates.

There was no significant difference in the solubility profiles (Figure 7 and 8) of triclosan combined with N-methylglucamine or L-arginine in both water and the buffer. Maximum solubilities achieved at corresponding concentrations of the solubilizers were also not significantly different (Table I).

EFFECT OF SOLUBILIZERS ON THE ANTIMICROBIAL ACTIVITY OF TRICLOSAN

Triclosan possesses bacteriostatic activity at low concentrations when tested against most gram-negative as well as gram-positive bacteria by the agar incorporation method, a notable exception being *Pseudomonas* (1). Since the solubilizers increased the solubility of triclosan in water, it is important to know if these solubilizers influenced the antimicrobiological activity of triclosan. Therefore, the antimicrobial activity of the five solubilizers that improved the solubility of triclosan in water the most, N-methylglucamine, L-arginine, ethanolamine, SLS, and βCD, were tested alone and in combination with triclosan against *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aereus, Aspergillus niger,* and *Candida albicans.*

The size of growth inhibition zones listed in Table II show that the solubilizer with the best bacteriostatic activity was SLS against *A. niger.* However, this compound did not inhibit the growth of *E. coli* or *P. aeruginosa.* Both N-methylglucamine and ethanolamine significantly inhibited the growth of all the organisms tested, while βCD showed no zone inhibition at all. Triclosan inhibited the growth of all the organisms tested except *P. aeruginosa.*

Statistically there were no significant differences between the growth inhibition zones

Table II
Antimicrobial Activity, Measured by Zone Inhibition, of Triclosan and Solubilizing Agents

Compound	Diameter of inhibition zone (mm)				
	E. coli	*P. aeruginosa*	*S. aureus*	*A. niger*	*C. albicans*
Triclosan powder	18.8	No zone	19.5	17.4	14.5
N-methylglucamine	15.9	19.3	14.3	25.5	20.9
L-arginine	No zone	14.7	No zone	24.6	20.1
Ethanolamine	23.9	24.6	12.9	27.8	18.4
SLS	No zone	No zone	18.2	28.6	15.1
βCD	No zone	No zone	No zone	No zone	No zone

for mixtures of triclosan and the solubilizing agents prepared in water or the pH 7.4 phosphate buffer. In Table III the results for the phosphate buffer solutions are listed. The diameters of the zones of inhibition increased when a constant concentration of 6.0 mg/ml^{-1} of triclosan was mixed with all the solubilizers. This showed that the bacteriostatic efficacy of triclosan increased when combined with the solubilizers. Whether this was because of the bacteriostatic efficacy of the solubilizer, or a synergistic effect that occurred, is unknown.

The results listed in Table III show that, on average, the combined solutions doubled the diameters of the inhibition zones. From these results, it is also clear that N-methylglucamine, L-arginine, and ethanolamine in combination with triclosan were the most effective antimicrobial combinations. Although not as effective as the other solubilizers, both βCD and SLS also enhanced the growth inhibition of most of the organisms tested when combined with triclosan. The difference between the antimicrobial activity of solutions containing the complexing agents, N-methylglucamine, L-arginine, and ethanolamine, and the compounds that encapsulate the triclosan, βCD and SLS, was significant. This difference could be the result of partial inactivation of the triclosan by micellar entrapping on inclusion because these processes reduce the amount of free triclosan available in solution. Overall, triclosan/solubilizer combinations were most effective against *A. niger* and least effective against *P. aeruginosa.*

CONCLUSIONS

A solubilization study for triclosan in water and pH 7.4 phosphate buffer at 30° C

Table III
Antimicrobial Activity, Measured by Zone Inhibition, of Solutions Prepared in pH 7.4 Phosphate Buffer Containing Triclosan and Solubilizing Agents

Compound	Diameter of inhibition zone (mm)				
	E. coli	*P. aeruginosa*	*S. aureus*	*A. niger*	*C. albicans*
N-methylglucamine	34.2	17.4	32.7	42.4	29.4
L-arginine	34.9	19.1	34.1	44.2	31.4
Ethanolamine	35.0	23.5	31.5	42.5	31.2
SLS	23.5	12.4	21.0	30.4	23.2
βCD	30.5	No zone	23.1	27.8	27.2

showed the following compounds as potential solubilizers of the drug. They are in order of their solubilizing performance: N-methylglucamine ≥ L-arginine > SLS > βCD ≥ HPβCD > ethanolamine > sodium benzoate > sodium methyl 4-hydroxybenzoate > triethanolamine ≥ diethanolamine. By using these solubilizers, the solubility of triclosan was increased 80- to 6000-fold. The formation of either salts or complexes is postulated as a possible mechanism for the increase in the solubility of triclosan by these compounds. In addition, the combination of triclosan with some of these solubilizers increased the antimicrobial potency of triclosan. The mechanism for this increase in activity is unknown and needs further investigation. However, complexing and salt-forming agents improved the activity of triclosan significantly more than compounds that solubilized triclosan by micellar or molecular inclusion.

REFERENCES

(1) C. A. Savage, A new bacteriostat for skin care products, *Drug Cosmet. Ind.,* **109,** 36–38, 163 (1971).

(2) H. P. Nissan and D. Ochs, Triclosan: An antimicrobial active ingredient with anti-inflammatory activity, *Cosmet. Toiletr.,* **113,** 61–64 (1998).

(3) V. Kjaerheim, P. Barkvoll, S. M. Waaler, and G. Roella, Triclosan inhibits histamine-induced inflammation in human skin, *J Clin. Periodont.,* **22,** 423–426 (1995).

(4) R. D. Jones, H. B. Jampani, J. L. Newman, and A. S. Lee, Triclosan: A review of effectiveness and safety in health care settings, *Am. J. Infect. Control.,* **28,** 184–196 (2000).

(5) S. M. Waaler, G. Roella, K. K. Skjoerland, and B. Oegaard, Effects of oral rinsing with triclosan and sodium lauryl sulphate on dental plaque formation: A pilot study, *Scand. J. Dent. Res.,* **101,** 192–195 (1993).

(6) V. Kjaerheim, S. M. Waaler, and A. Kalvik, Experiments with two-phase plaque-inhibiting mouthrinses, *Eur. J. Oral Sci.,* **103,** 179–181 (1995).

(7) L. M. McMurry, M. Oethinger, and S. B. Levy, Triclosan targets lipid synthesis, *Nature,* **394,** 531–532 (1998).

(8) C. W. Levy, A. Roujeinikova, S. Sedelnikova, P. J. Baker, A. R. Stuitje, A. R. Slabas, D. W. Rice, and J. B. Rafferty, Molecular basis of triclosan activity, *Nature,* **398,** 383–384 (1999).

(9) S. Namita and A. Surolia, Triclosan offers protection against blood stages of malaria by inhibiting enol-ACP reductase of *Plasmodium falciparum, Nat. Med.,* **7,** 167–173 (2001).

(10) R. Perozzo, M. Kuo, A. S. Sidhu, J. T. Valiyaveetti, R. Bittman, W. R. Jacobs, D. A. Fidock, and J. C. Sacchettini, Structural elucidation of the specificity of the antibacterial agent triclosan for malarial enoyl acyl carrier protein reductase, *J. Biol. Chem.,* 277, 13106–13114 (2002).

(11) T. Loftsson, N. Leeves, N. Bjornsdottir, L. Duffy, and M. Masson, Effect of cyclodextrins and polymers on triclosan availability and substantivity in toothpastes *in vivo, J. Pharm. Sci.,* **88,** 1254–1258 (1999).

(12) S. H. Yalkowsky, Ed., *Techniques of Solubilization of Drugs* (Marcel Dekker, New York, 1981), pp. 16–34, 91–134, 135–157.

(13) J. Lu, M. A. Hill, M. Hood, D. F. Greeson, J. R. Horton, P. E. Orndorff, A. S. Herndon, and A. E. Tonelli, Formation of antibiotic, biodegradable polymers by processing with Irgasan DP 300R (triclosan) and its inclusion compound with β-cyclodextrin, *J. Fiber Polym. Sci.,* **82,** 300–309 (2001).

(14) P. M. Ashall, B. M. Kiernan, and N. R. Russell, Complexation of the bacteriostat triclosan the γ-cyclodextrin, *Proceedings of the World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Budapest, May 9–11, 1995,* pp. 605–606.

(15) T. Loftsson, N. Leeves, J. F. Sigurjonsdottir, H. H. Sigurosson, and M. Masson, Sustained drug delivery system based on a cationic polymer and an anionic drug/cyclodextrin complex, *Pharmazie,* **56,** 746–747 (2001).

(16) *The United States Pharmacopeia,* XXIVth Revision (United States Pharmacopeial Convention, Rockville, MD, 2000).

(17) J. K. Lim, H. O. Thompson, and C. Piantadosi, Solubilization and stability of phenobarbital by some aminoalcohols, *J. Pharm. Sci.,* **53,** 1161–1165 (1964).

(18) M. M. de Villiers, W. Liebenberg, S. F. Malan, and J. J. Gerber, The dissolution and complexing properties of ibuprofen and ketoprofen when mixed with N-methylglucamine, *Drug Dev. Ind. Pharm.,* **25,** 967–972 (1999).
(19) A. Al-Maaieh and D. R. Flanagan, Salt effects on caffeine solubility, distribution, and self-association, *J. Pharm. Sci.,* **91,** 1000–1008 (2002).
(20) K. R. Morris, M. G. Fakes, A. B. Thakur, A. W. Newman, A. K. Singh, J. J. Venit, C. J. Spagnuolo, and A. T. M. Serajuddin, An integrated approach to the selection of optimal salt form for a new drug candidate, *Int. J. Pharm.,* **105,** 209–217 (1994).